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TO: Andrew D Kosar
Location: REM 3C18/3C04
Art Unit: 1654
November 26, 2004

Case Serial Number: 10/663220

From: P. Sheppard
Location: Remsen Building
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sheppard@uspto.gov

Search Notes

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:32:46 ON 26 NOV 2004
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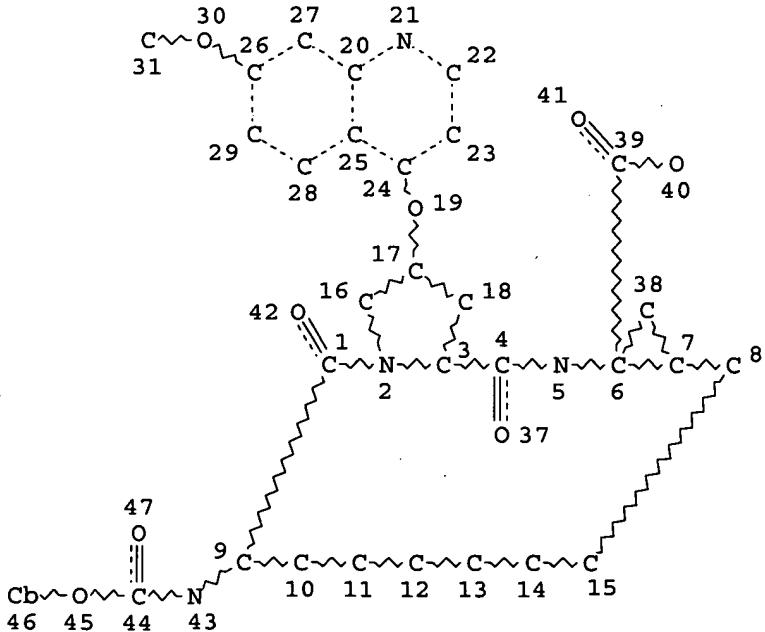
FILE COVERS 1907 - 26 Nov 2004 VOL 141 ISS 22
FILE LAST UPDATED: 24 Nov 2004 (20041124/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L3 STR



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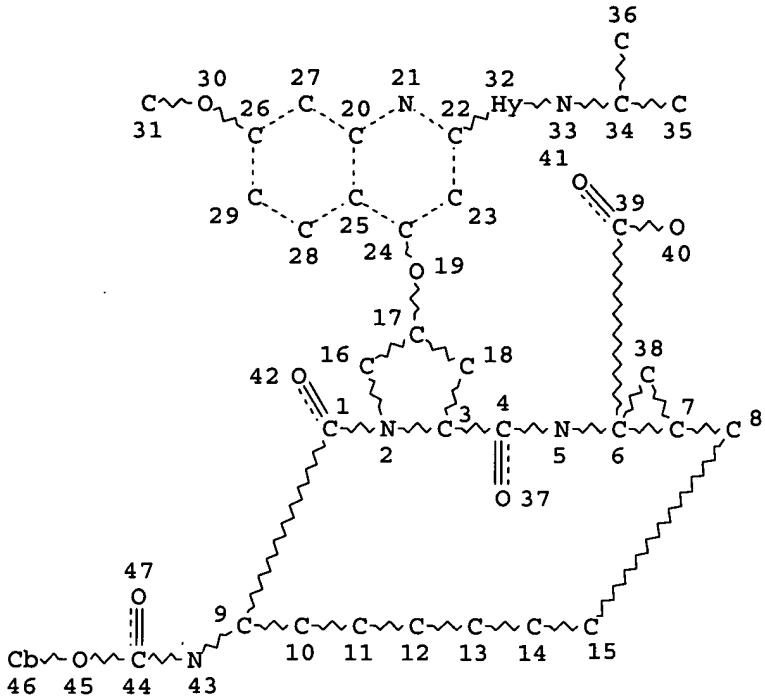
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 42

STEREO ATTRIBUTES: NONE

L5 56 SEA FILE=REGISTRY SSS FUL L3
L6 STR

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE

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L8 19 SEA FILE=HCAPLUS ABB=ON PLU=ON L7

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=> d ibib abs hitstr 18 1-19

L8 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:940427 HCAPLUS

TITLE: The design of a potent inhibitor of the hepatitis C virus NS3 protease: BILN 2061 - From the NMR tube to the clinic

AUTHOR(S): Tsantrizos, Youla S.

CORPORATE SOURCE: Research and Development, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.

SOURCE: Biopolymers (2004), 76(4), 309-323
CODEN: BIPMAA; ISSN: 0006-3525

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The virally encoded serine protease NS3/NS4A is essential to

the life cycle of the hepatitis C virus (HCV), an important human pathogen causing chronic hepatitis, cirrhosis of the liver, and hepatocellular carcinoma. Until very recently, the design of inhibitors for the HCV NS3 protease was limited to large peptidomimetic compds. with poor pharmacokinetic properties, making drug discovery an extremely challenging endeavor. In our quest for the discovery of a small-mol. lead that could block replication of the hepatitis C virus by binding to the HCV NS3 protease, the critical protein-polypeptide interactions between the virally encoded NS3 serine protease and its polyprotein substrate were investigated. Lead optimization of a substrate-based hexapeptide, guided by structural data, led to the understanding of the mol. dynamics and electronic effects that modulate the affinity of peptidomimetic ligands for the active site of this enzyme. Macroyclic β -strand scaffolds were designed that allowed the discovery of potent, highly selective, and orally bioavailable compds. These mols. were the first HCV NS3 protease inhibitors reported that inhibit replication of HCV subgenomic RNA in a cell-based replicon assay at low nanomolar concns. Optimization of their biopharmaceutical properties led to the discovery of the clin. candidate BILN 2061. Oral administration of BILN 2061 to patients infected with the hepatitis C genotype 1 virus resulted in an impressive reduction of viral RNA levels, establishing proof-of-concept for HCV NS3 protease inhibitors as therapeutic agents in humans.

IT 300832-84-2, BILN 2061

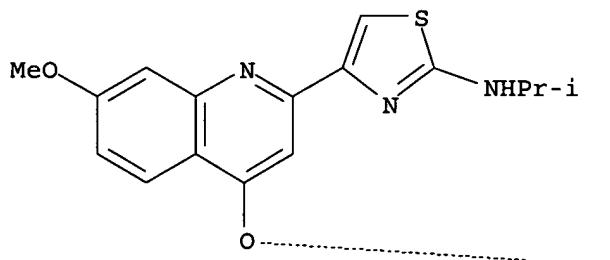
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design of potent inhibitor of hepatitis C virus NS3 protease BILN
2061: from NMR tube to clinic)

RN 300832-84-2 HCPLUS

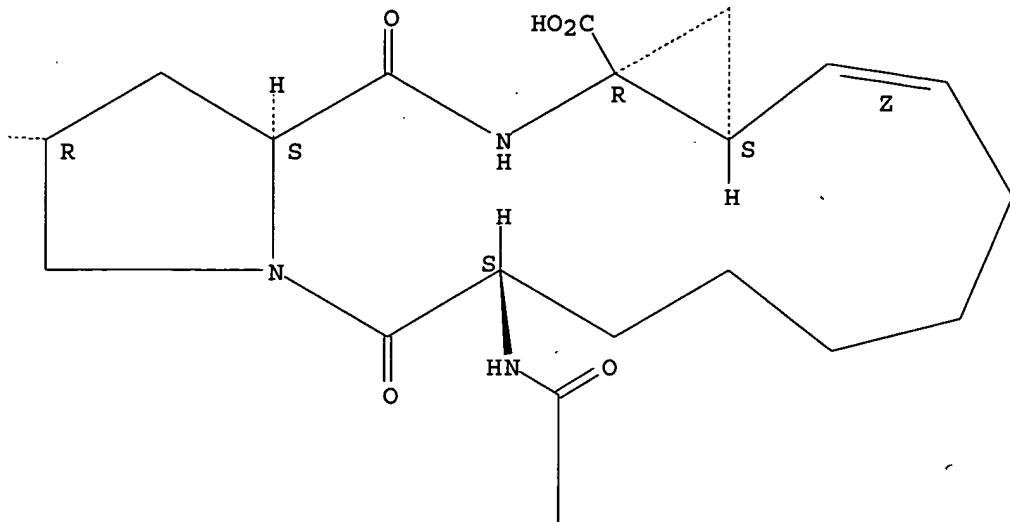
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

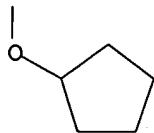
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:927080 HCAPLUS
 TITLE: Pharmaceutical compositions for hepatitis C viral protease inhibitors
 INVENTOR(S): Chen, Shirlynn; Mei, Xiaohui; Wang, Zeren
 PATENT ASSIGNEE(S): Boehringer Ingelheim International, G.m.b.H., Germany
 SOURCE: PCT Int. Appl., 60 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004093915	A1	20041104	WO 2004-US8837	20040323
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,				

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
 SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
 TD, TG

US 2004229776 A1 20041118 US 2004-807023 20040323

US 2003-459765P P 20030402

PRIORITY APPLN. INFO.:

AB Disclosed are pharmaceutical compns. of hepatitis C viral protease inhibitors, and methods of using these compns. for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compns. are lipid based systems and comprise the hepatitis C viral protease inhibitor together with at least one pharmaceutically acceptable amine, at least one pharmaceutically acceptable base, at least one pharmaceutically acceptable oil and optionally one or more addnl. ingredients. For example, a formulation was prepared containing hepatitis C protease inhibitor 10, tromethamine 1, sodium hydroxide 0.3, water 1.7, ethanol 10, propylene glycol 5, α -tocopherol 0.4, Capmul MCM 22, and TPGS 49.6%, resp. The formulation can be filled into hard shell or soft gelatin capsules.

IT 300832-84-2

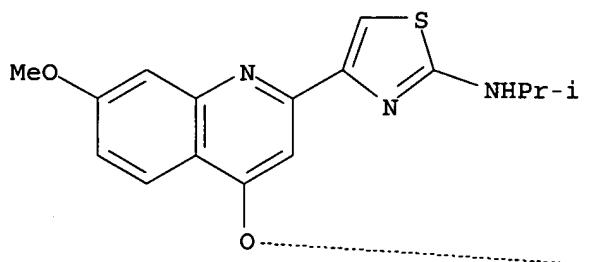
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (oral compns. for hepatitis C viral protease inhibitors)

RN 300832-84-2 HCPLUS

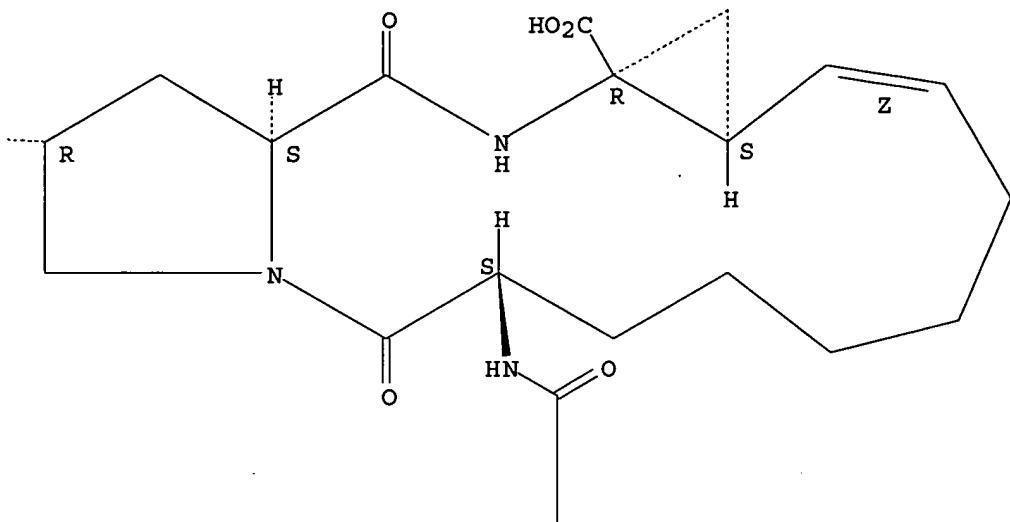
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

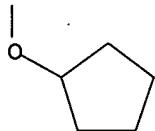
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:905774 HCAPLUS
 TITLE: Process for preparing macrocyclic compounds
 INVENTOR(S): Donsbach, Kai; Ecker, Dieter; Frutos, Rogelio Perez;
 Gallou, Fabrice; Gutheil, Dieter; Haddad, Nizar;
 Hagenkoetter, Robert; Kemmer, Dirk; Kroeber, Jutta;
 Nicola, Thomas; Schnaubelt, Juergen; Schul, Michael;
 Simpson, Robert Donald; Wei, Xudong; Winter, Eric; Xu, Yibo; Yee, Nathan K.; Brandenburg, Joerg
 PATENT ASSIGNEE(S): Boehringer Ingelheim International, G.m.b.H., Germany;
 Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
 SOURCE: PCT Int. Appl., 59 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092203	A2	20041028	WO 2004-US10476	20040406

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
 CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
 SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
 TD, TG

PRIORITY APPLN. INFO.:
 GI

US 2003-461662P P 20030410

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed is a process for preparing macrocyclic compds. I [W is CH or N; R1 is H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy or an amino group; R2 is H, halo, alkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, (un)substituted cycloalkyl, aryl or heterocycl; R3 is OH, NH2, aryl-, heteroaryl- or acylamino; D is alkylene which may be substituted by R4 (alkyl, alkoxy, halo, amino, etc.); A is CO2H or an amide or salt] which are potent active agents for the treatment of hepatitis C virus (HCV) infection. The process involves reaction of a 4-hydroxyproline sulfonate macrocycle with a 4-naphthol or 4-quinolinol derivative and was applied to the synthesis of II by a multistep sequence.

IT 681145-22-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

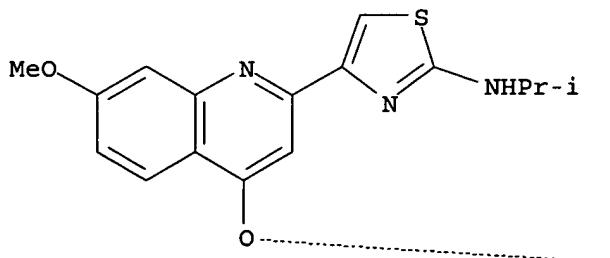
(process for preparing macrocyclic compds.)

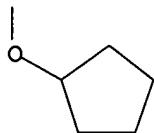
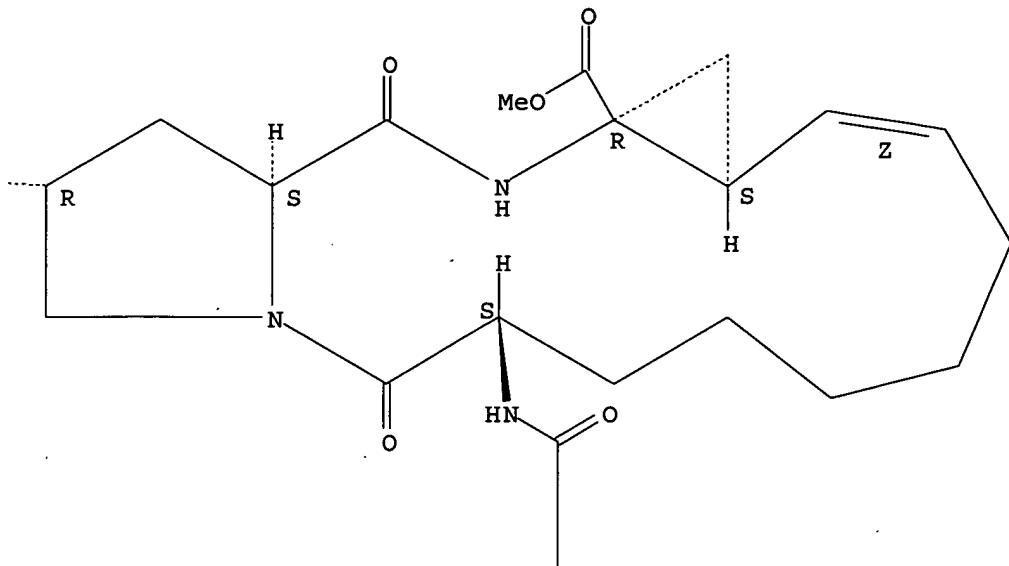
RN 681145-22-2 HCPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, methyl ester, (2R,6S,12Z,13aS,14aR,16aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

PAGE 1-A





IT 300832-84-2P

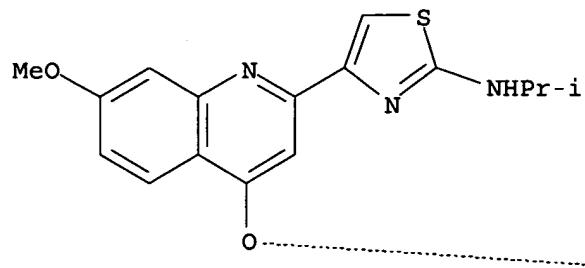
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparing macrocyclic compds.)

RN 300832-84-2 HCPLUS

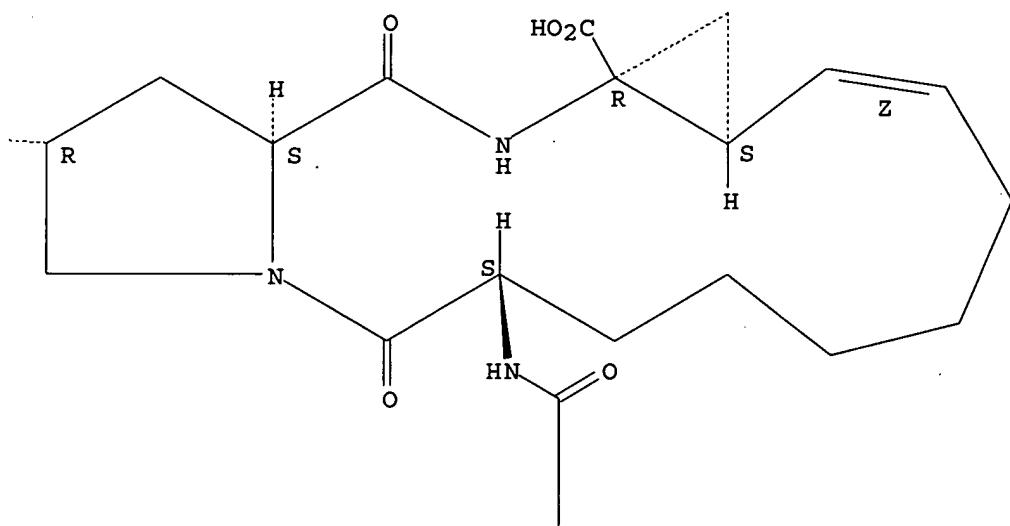
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

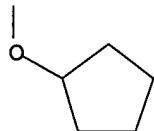
PAGE 1-A



PAGE 1-B



PAGE 2-B



L8 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:857622 HCAPLUS
 DOCUMENT NUMBER: 141:337786
 TITLE: Crystalline phases of a potent HCV inhibitor
 INVENTOR(S): Cerreta, Michael Kenneth; Smoliga, John Andrew;
 Varsolona, Richard J.
 PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
 SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

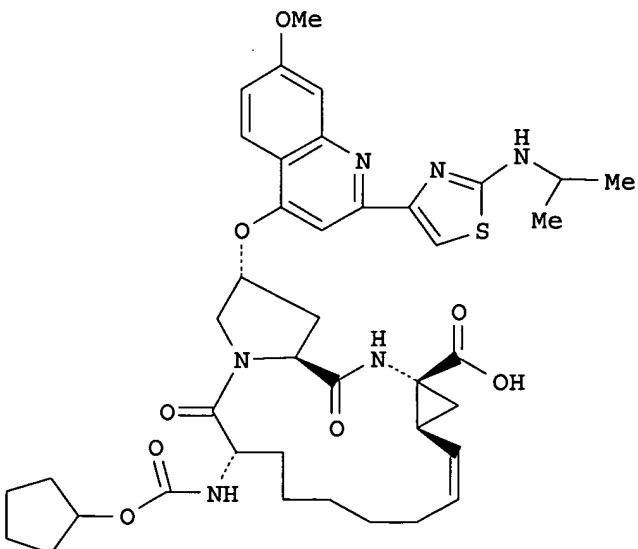
English

FAMILY ACC. NUM. COUNT:

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PATENT INFORMATION:

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WO 2004087741	A1	20041014	WO 2004-US9085	20040325
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004229777	A1	20041118	US 2004-809597	20040325
PRIORITY APPLN. INFO.:			US 2003-458188P	P 20030327
GI				



AB This invention relates to novel crystalline phases of Compound (I), methods for the preparation thereof, pharmaceutical compns. thereof, and their use in the treatment of Hepatitis C Viral (HCV) infection.

IT 300832-84-2P

RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(crystalline phases of a potent HCV inhibitor)

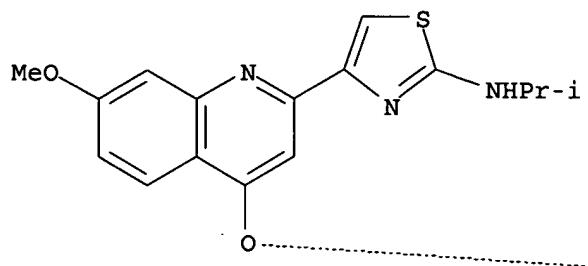
RN 300832-84-2 HCAPLUS

CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[cyclopentyloxy]carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16

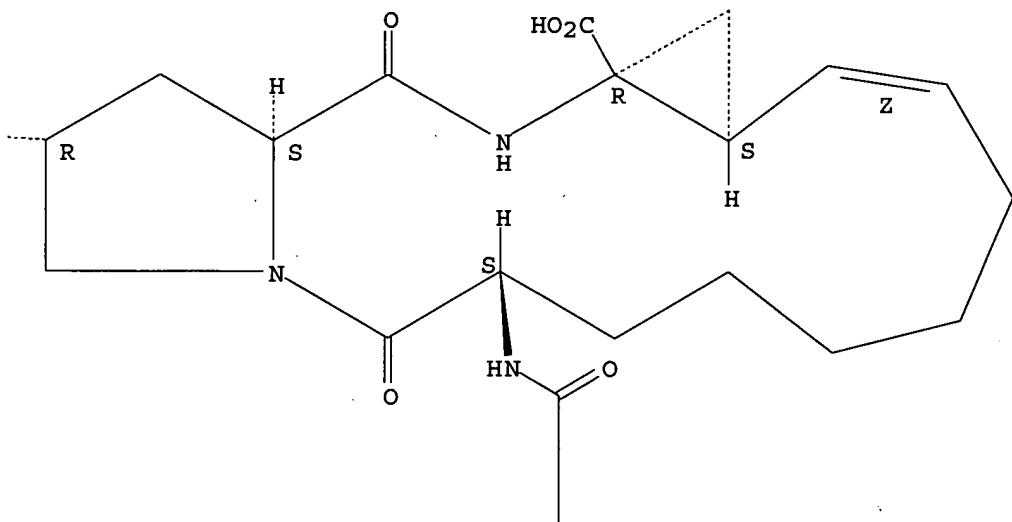
,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

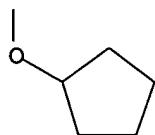
PAGE 1-A



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PAGE 2-B



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:590266 HCAPLUS
 DOCUMENT NUMBER: 141:184653
 TITLE: Sensitivity of NS3 serine proteases from hepatitis C
 virus genotypes 2 and 3 to the inhibitor BILN 2061
 AUTHOR(S): Thibeault, Diane; Bousquet, Christiane; Gingras, Rock;
 Lagace, Lisette; Maurice, Roger; White, Peter W.;
 Lamarre, Daniel
 CORPORATE SOURCE: Department of Biological Sciences, Research and
 Development, Boehringer Ingelheim (Canada) Ltd.,
 Laval, QC, H7S 2G5, Can.
 SOURCE: Journal of Virology (2004), 78(14), 7352-7359
 CODEN: JOVIAM; ISSN: 0022-538X
 PUBLISHER: American Society for Microbiology
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Hepatitis C virus (HCV) displays a high degree of genetic variability. Six genotypes and more than 50 subtypes have been identified to date. In this report, kinetic profiles were determined for NS3 proteases of genotypes 1a, 1b, 2ac, 2b, and 3a, revealing no major differences in activity. In vitro sensitivity studies with BILN 2061 showed a decrease in affinity for proteases of genotypes 2 and 3 (K_i , 80 to 90 nM) compared to genotype 1 enzymes (K_i , 1.5 nM). To understand the reduced sensitivity of genotypes 2 and 3 to BILN 2061, active-site residues in the proximity of the inhibitor binding site were replaced in the genotype-1b enzyme with the corresponding genotype-2b or -3a residues. The replacement of five residues at positions 78, 79, 80, 122, and 132 accounted for most of the reduced sensitivity of genotype 2b, while replacement of residue 168 alone could account for the reduced sensitivity of genotype 3a. BILN 2061 remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins, with K_i values below 100 nM. This in vitro potency, in conjunction with the good pharmacokinetic data reported for humans, suggests that there is potential for BILN 2061 as an antiviral agent for individuals infected with non-genotype-1 HCV.

IT 300832-84-2, BILN 2061

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

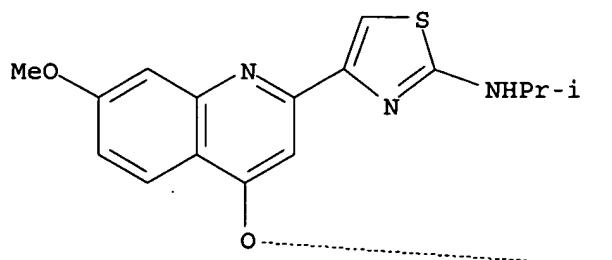
(HCV genotypes 2 and 3 NS3 serine proteases sensitive to inhibitor BILN 2061)

RN 300832-84-2 HCAPLUS

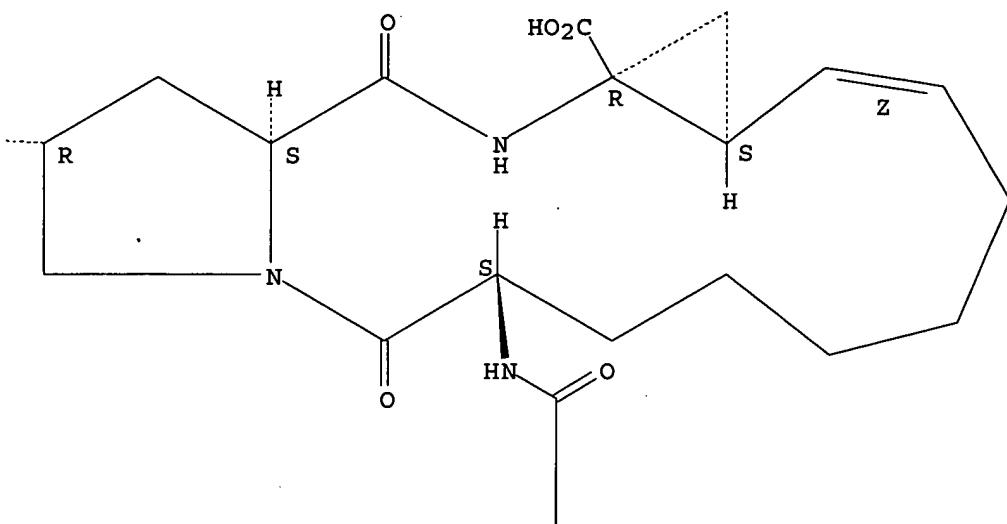
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

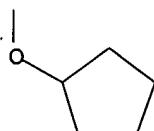
PAGE 1-A



PAGE 1-B

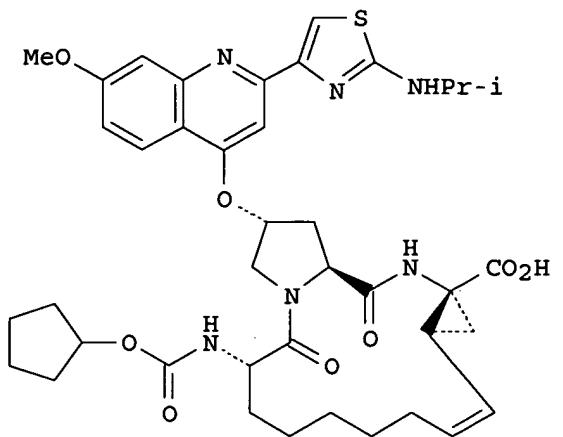


PAGE 2-B



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:580783 HCAPLUS
 DOCUMENT NUMBER: 141:261053
 TITLE: Synthesis of BILN 2061, an HCV NS3 Protease Inhibitor with Proven Antiviral Effect in Humans
 AUTHOR(S): Faucher, Anne-Marie; Bailey, Murray D.; Beaulieu, Pierre L.; Brochu, Christian; Duceppe, Jean-Simon; Ferland, Jean-Marie; Ghiro, Elise; Gorys, Vida; Halmos, Ted; Kawai, Stephen H.; Poirier, Martin; Simoneau, Bruno; Tsantrizos, Youla S.; Llinas-Brunet, Montse
 CORPORATE SOURCE: Chemistry Department, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
 SOURCE: Organic Letters (2004), 6 (17), 2901-2904
 CODEN: ORLEF7; ISSN: 1523-7060
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The synthesis of BILN 2061 (I), a hepatitis C virus (HCV) NS3 protease inhibitor with proven antiviral effect in humans, was accomplished in a convergent manner from four building blocks. The procedure described here was suitable for the preparation of multigram quantities of BILN 2061 for preclin. pharmacol. evaluation.

IT 300832-84-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

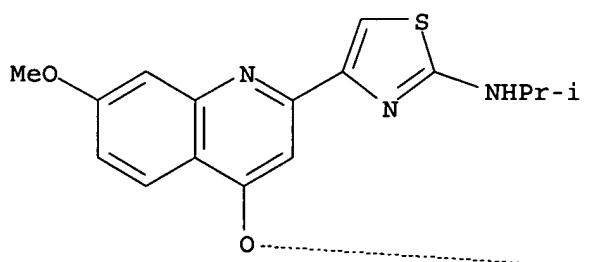
(preparation of peptidyl macrocycle BILN-2061, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

RN 300832-84-2 HCPLUS

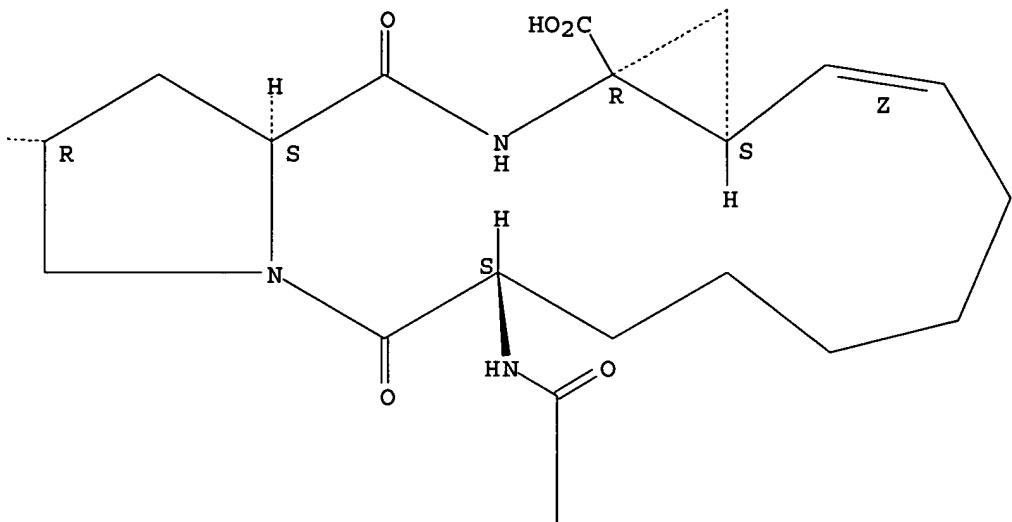
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Absolute stereochemistry.
Double bond geometry as shown.

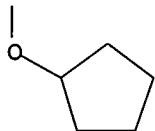
PAGE 1-A



PAGE 1-B



PAGE 2-B



IT 681145-22-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

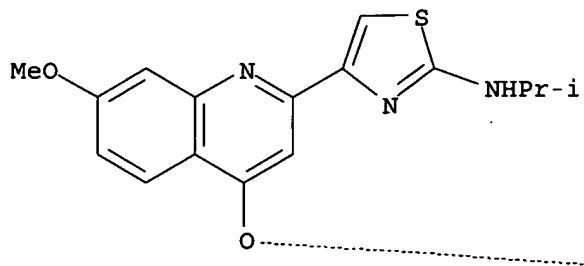
(preparation of peptidyl macrocycle BILN-2061, an HCV NS3 protease inhibitor with proven antiviral effect in humans)

RN 681145-22-2 HCPLUS

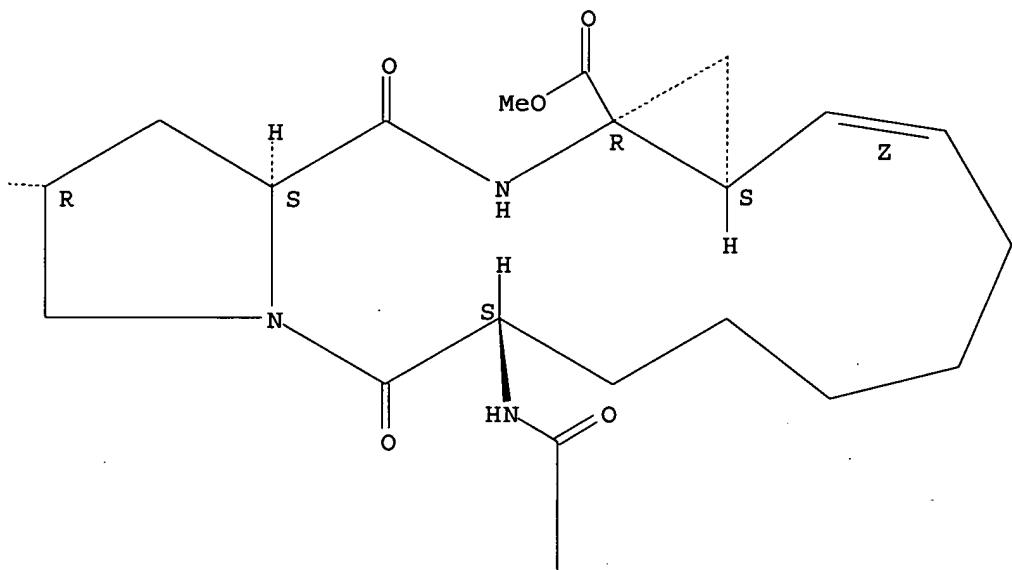
CN Cyclopropane[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*(5*H*)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13*a*,14,15,16,16*a*-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, methyl ester, (2*R*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

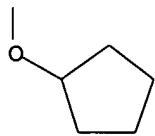
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT:

39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:468978 HCAPLUS

DOCUMENT NUMBER: 141:220806

TITLE: Mutations conferring resistance to a potent hepatitis C virus serine protease inhibitor in vitro

AUTHOR(S): Lu, Liangjun; Pilot-Matias, Tami J.; Stewart, Kent D.;

Randolph, John T.; Pithawalla, Ron; He, Wenping;
 Huang, Peggy P.; Klein, Larry L.; Mo, Hongmei; Molla,
 Akhteruzzaman

CORPORATE SOURCE: Antiviral Research, Global Pharmaceutical Research and Development, Abbott Park, IL, USA

SOURCE: Antimicrobial Agents and Chemotherapy (2004), 48(6), 2260-2266

PUBLISHER: CODEN: AMACQ; ISSN: 0066-4804

DOCUMENT TYPE: American Society for Microbiology

LANGUAGE: Journal English

AB BILN 2061 is a novel, specific hepatitis C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clin. investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of drug-resistant viruses in treated patients. The development of resistance to BILN 2061 was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concns. of BILN 2061 for these colonies were 72- to 1228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Mol. clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold redns. in susceptibility to BILN 2061, resp., compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure anal. of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

IT 300832-84-2, BILN 2061

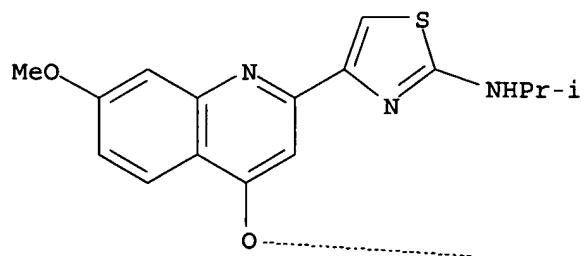
RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (mutations conferring inhibitor resistance on hepatitis C virus serine protease)

RN 300832-84-2 HCAPLUS

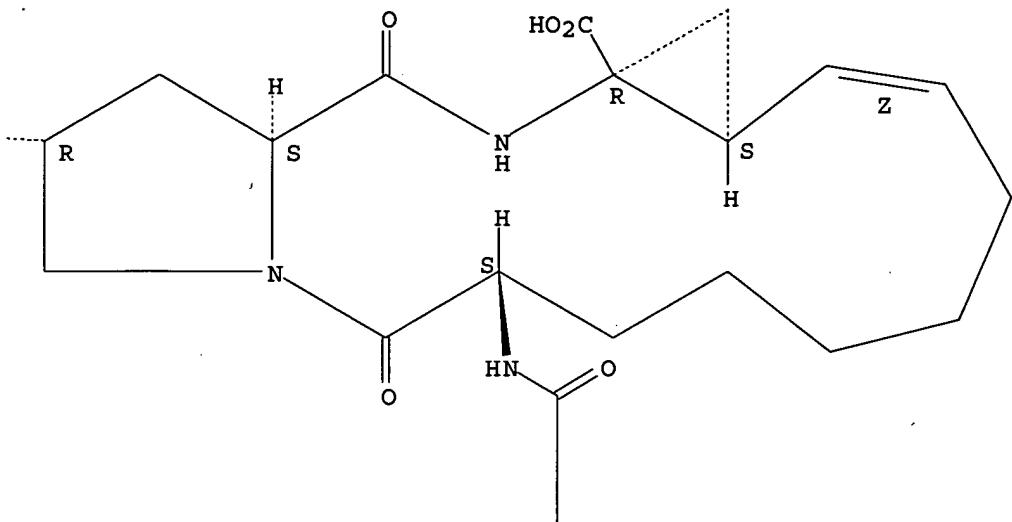
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

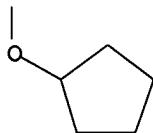
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:392478 HCAPLUS
 DOCUMENT NUMBER: 140:400031
 TITLE: Macroyclic compound-containing compositions for the treatment of infection by Flaviviridae viruses
 INVENTOR(S): Lamarre, Daniel; Lagace, Lisette
 PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
 SOURCE: PCT Int. Appl., 57 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039833	A1	20040513	WO 2003-CA1634	20031024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,				

OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
 TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
 NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
 GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

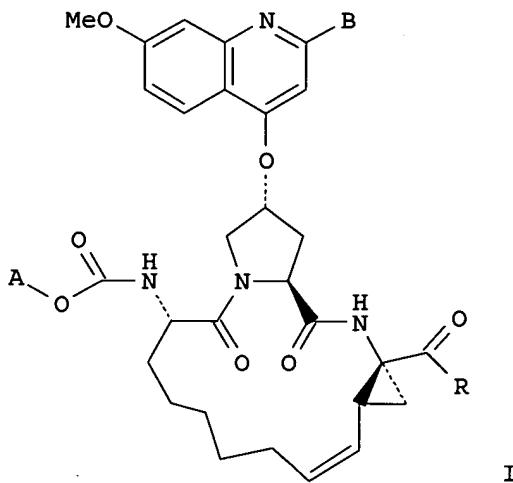
US 2002-421900P P 20021029

US 2003-442769P P 20030127

OTHER SOURCE(S):

MARPAT 140:400031

GI



AB The invention relates to macrocyclic compds. I [A is alkyl or cycloalkyl; B is Ph or thiazolyl, which may be substituted by alkylamino or alkanoylamino; R is OH or NHSO_2R_2 , where R_2 is (un)substituted alkyl, cycloalkyl or aryl] or their pharmaceutically-acceptable salts for the treatment of a mammal infected with a virus of the Flaviviridae family. Thus, IC₅₀ values for compound I [A is cyclopentyl, B is 2-(isopropylamino)-4-thiazolyl, R is OH] against HCV NS3-NS4A protease are shown graphically.

IT 300832-84-2

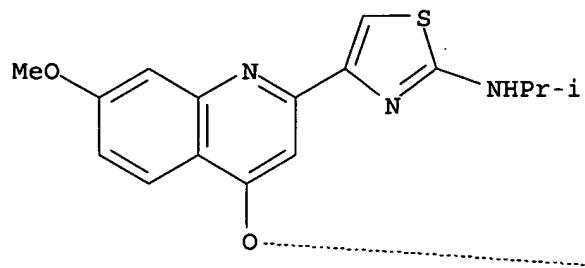
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

RN 300832-84-2 HCPLUS

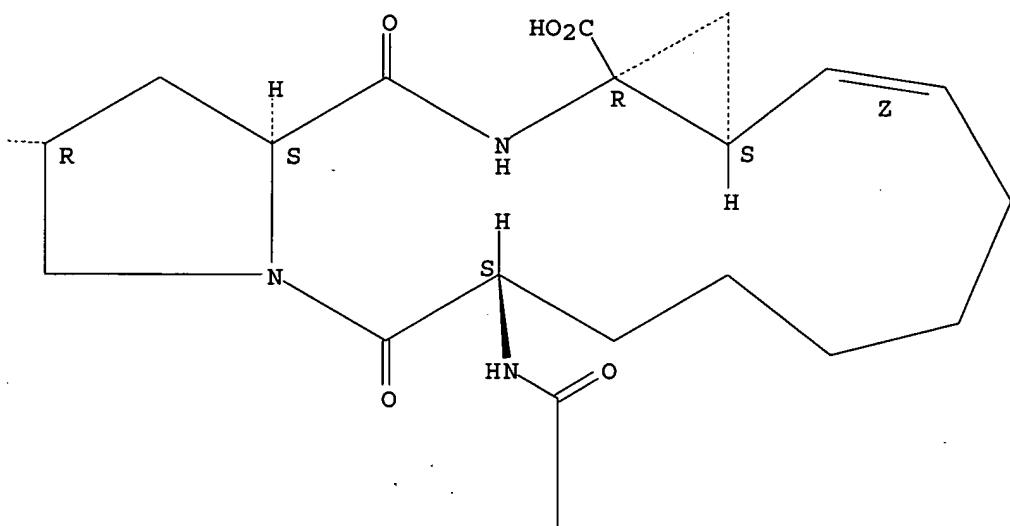
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Absolute stereochemistry.
 Double bond geometry as shown.

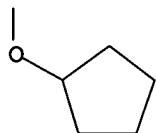
PAGE 1-A



PAGE 1-B



PAGE 2-B



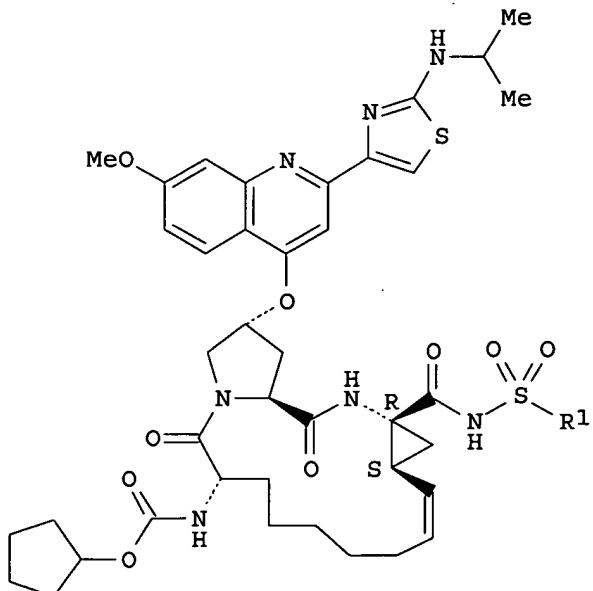
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:370958 HCAPLUS
 DOCUMENT NUMBER: 140:357673
 TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
 INVENTOR(S): Llinas-Brunet, Montse; Bailey, Murray D.

PATENT ASSIGNEE(S) : Boehringer Ingelheim International G.m.b.h., Germany
 SOURCE: PCT Int. Appl., 40 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037855	A1	20040506	WO 2003-CA1604	20031020
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2002-421414P	P 20021025
			US 2002-433820P	P 20021216
			US 2003-442768P	P 20030127

OTHER SOURCE(S) : MARPAT 140:357673
 GI



AB Macrocyclic peptides I [R1 is (un)substituted alkyl, cycloalkyl, alkylcycloalkyl, aryl or heteroaryl] or their pharmaceutically-acceptable salts were prepared as inhibitors of the hepatitis C virus (HCV) NS3 protease. Thus, I (R = Me) was prepared by a multistep sequence involving peptide coupling, olefin metathesis to form the macrocycle and methanesulfonamidation.

IT 300832-84-2P 681145-22-2P

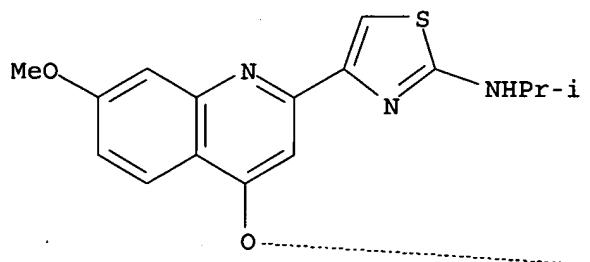
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of macrocyclic peptides active against the hepatitis C virus)

RN 300832-84-2 HCPLUS

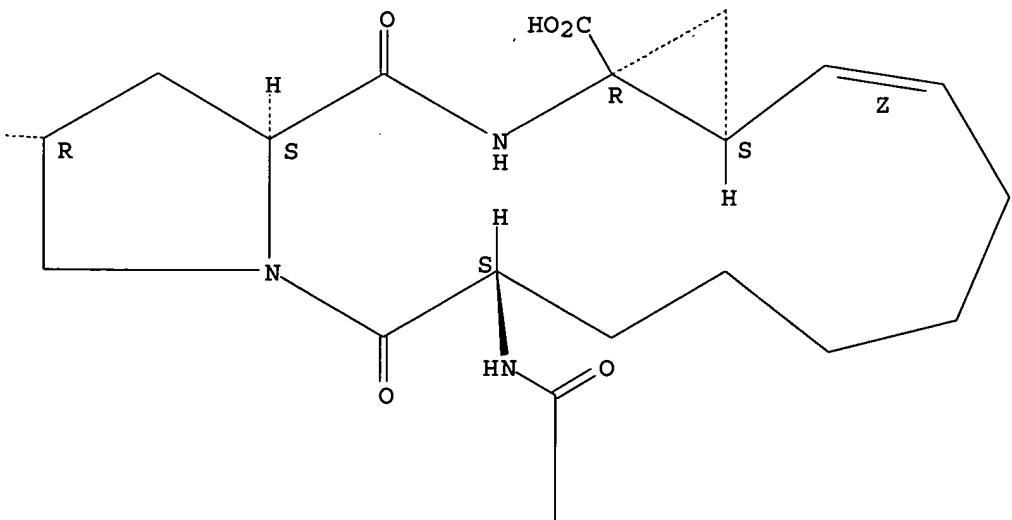
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[cyclopentyloxy]carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

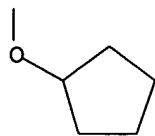
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PAGE 2-B

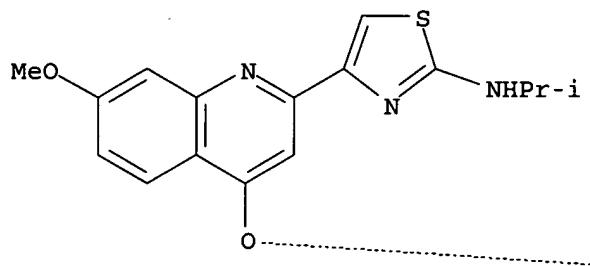


RN 681145-22-2 HCAPLUS

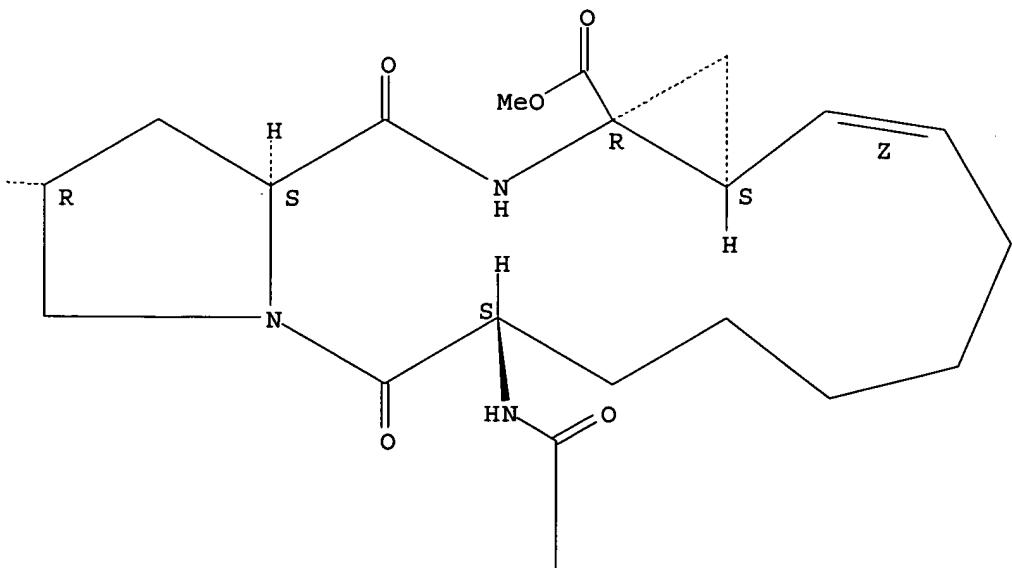
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[cyclopentyloxy]carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, methyl ester, (2R,6S,12Z,13aS,14aR,16aS)-(9CI) (CA INDEX NAME)

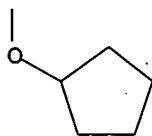
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

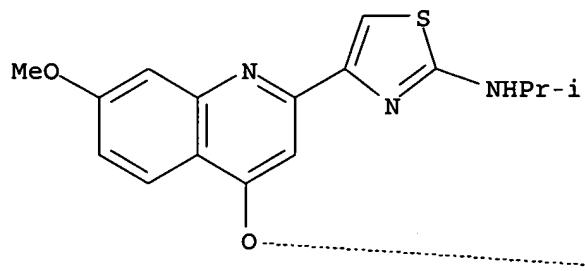




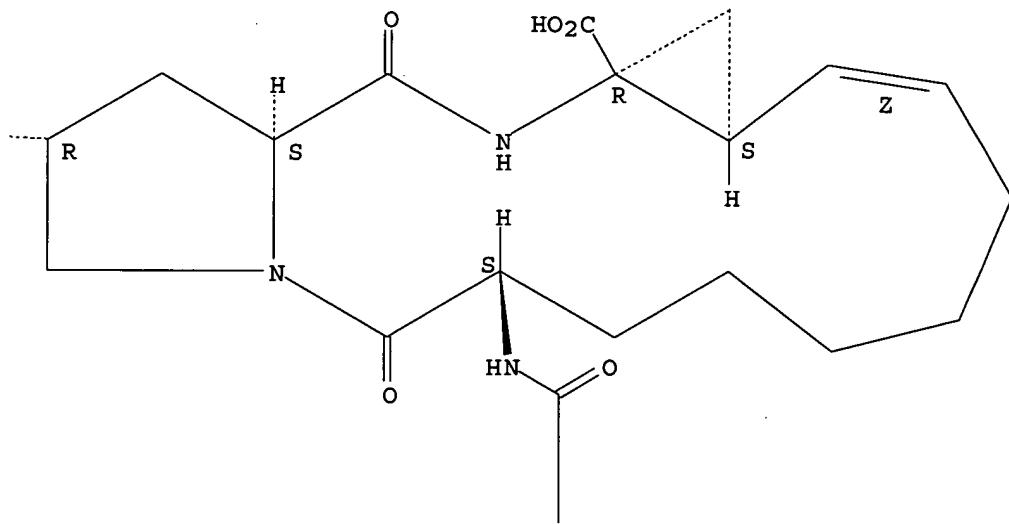
L8 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:325457 HCAPLUS
 DOCUMENT NUMBER: 141:16899
 TITLE: In Vitro Resistance Studies of Hepatitis C Virus Serine Protease Inhibitors, VX-950 and BILN 2061: structural analysis indicates different resistance mechanisms
 AUTHOR(S): Lin, Chao; Lin, Kai; Luong, Yu-Ping; Rao, B. Govinda; Wei, Yun-Yi; Brennan, Debra L.; Fulghum, John R.; Hsiao, Hsun-Mei; Ma, Sue; Maxwell, John P.; Cottrell, Kevin M.; Perni, Robert B.; Gates, Cynthia A.; Kwong, Ann D.
 CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, MA, 02139, USA
 SOURCE: Journal of Biological Chemistry (2004), 279(17), 17508-17514
 CODEN: JBCHA3; ISSN: 0021-9258
 PUBLISHER: American Society for Biochemistry and Molecular Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB We have used a structure-based drug design approach to identify small mol. inhibitors of the hepatitis C virus (HCV) NS3·4A protease as potential candidates for new anti-HCV therapies. VX-950 is a potent NS3·4A protease inhibitor that was recently selected as a clin. development candidate for hepatitis C treatment. In this report, we describe in vitro resistance studies using a subgenomic replicon system to compare VX-950 with another HCV NS3·4A protease inhibitor, BILN 2061, for which the Phase I clin. trial results were reported recently. Distinct drug-resistant substitutions of a single amino acid were identified in the HCV NS3 serine protease domain for both inhibitors. The resistance conferred by these mutations was confirmed by characterization of the mutant enzymes and replicon cells that contain the single amino acid substitutions. The major BILN 2061-resistant mutations at Asp168 are fully susceptible to VX-950, and the dominant resistant mutation against VX-950 at Ala156 remains sensitive to BILN 2061. Modeling anal. suggests that there are different mechanisms of resistance to VX-950 and BILN 2061.
 IT 300832-84-2, BILN 2061
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (structure-activity relationship and in vitro antiviral resistance studies of hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061)
 RN 300832-84-2 HCAPLUS
 CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[cyclopentyloxy]carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[1-methylethyl]amino]-4-thiazolyl]4-quinolinyloxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

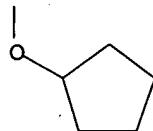
PAGE 1-A



PAGE 1-B



PAGE 2-B



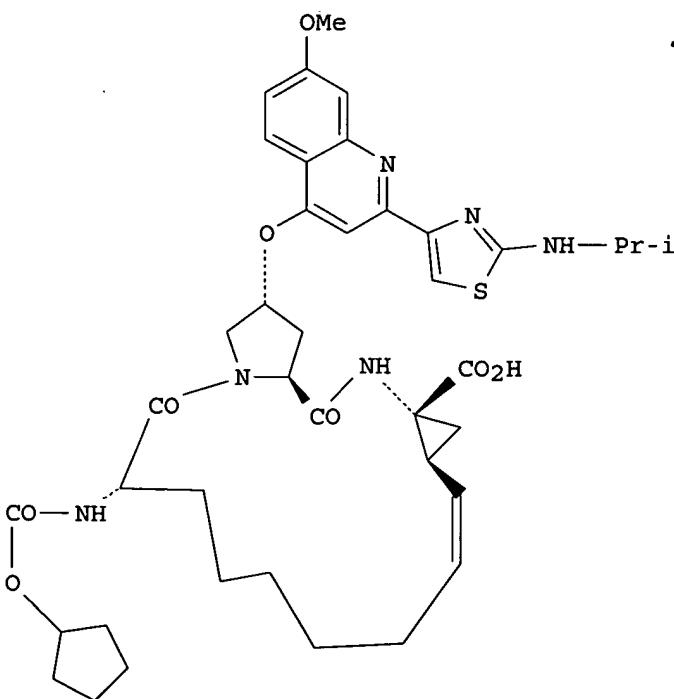
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 19 HCPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:310970 HCPLUS
 DOCUMENT NUMBER: 140:327091
 TITLE: Potent inhibitor of HCV serine protease
 INVENTOR(S): Chen, Shirlynn; Nehmiz, Gerhard; Croenlein, Jens
 Oliver; Steinmann, Gerhard; Gunn, Jocelyn Abella;
 Costa, Phuong Do

PATENT ASSIGNEE(S) : Boehringer Ingelheim International G.m.b.H., Germany
 SOURCE: PCT Int. Appl., 42 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004030670	A1	20040415	WO 2003-US30402	20030925
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004138109	A1	20040715	US 2003-663220	20030916
PRIORITY APPLN. INFO.:			US 2002-414940P	P 20020930
			US 2002-421904P	P 20021029
			US 2002-433834P	P 20021216
			US 2003-443662P	P 20030130

GI



AB Disclosed are oral pharmaceutical compns., kits and methods of treating and preventing Hepatitis C Viral (HCV) infections wherein Compound (I), a

potent inhibitor of HCV serine protease, or a pharmaceutically acceptable salt thereof, is administered in a selected dosage range. Also disclosed are the use of I or a pharmaceutically acceptable salt thereof, as a control substance for validating an HCV replication assay and also as a control substance for determining the relative effectiveness of one or more substances, alone or in combination, to inhibit the replication of HCV.

IT 300832-84-2

RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

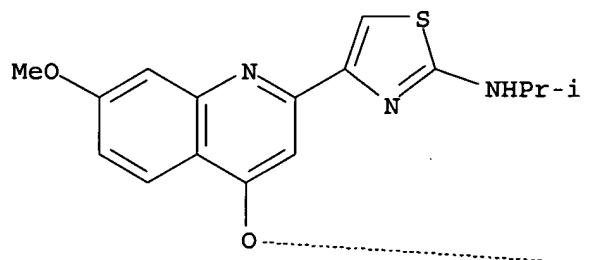
(potent inhibitor of HCV serine protease)

RN 300832-84-2 HCPLUS

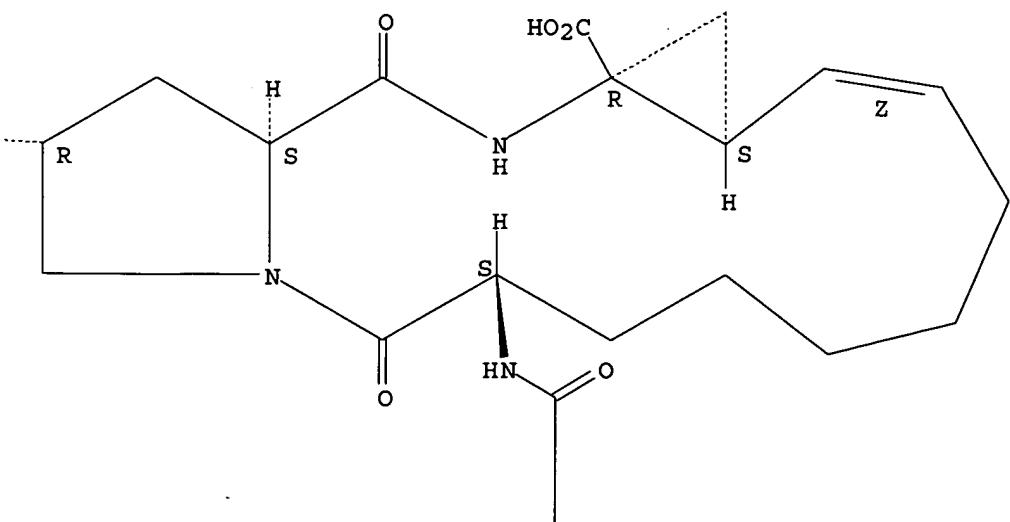
Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

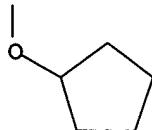
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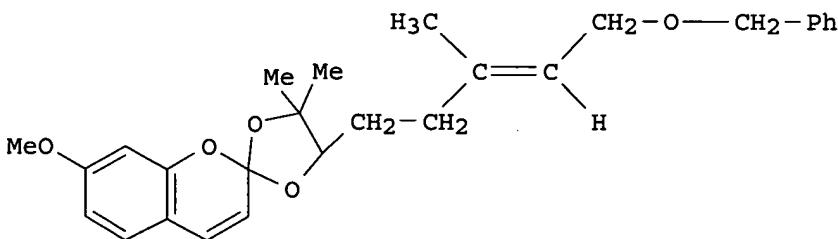


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:252197 HCAPLUS
 DOCUMENT NUMBER: 140:281350
 TITLE: Spiro compounds for inhibiting the first-pass effect
 INVENTOR(S): Harris, James W.
 PATENT ASSIGNEE(S): Bioavailability System, LLC, USA
 SOURCE: U.S. Pat. Appl. Publ., 133 pp., Cont.-in-part of U.S. Ser. No. 793,416.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 5
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058982	A1	20040325	US 2003-422848	20030425
US 6248776	B1	20010619	US 1999-251467	19990217
US 6476066	B1	20021105	US 2001-793416	20010227
PRIORITY APPLN. INFO.:			US 1999-251467	A3 19990217
			US 2001-793416	A2 20010227
			US 1997-56382P	P 19970826
			US 1997-997259	A2 19971223

OTHER SOURCE(S): MARPAT 140:281350
 GI



I

AB Compns., methods, etc. for addressing the first-pass effect are presented. An example compound prepared was I. Also processing citrus oils to obtain the compds. is given as examples as well as assessment of human cytochrome P 450-mediated biotransformation.

IT 300832-84-2, BILN 2061
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (spiro compds. for inhibiting the first-pass effect)

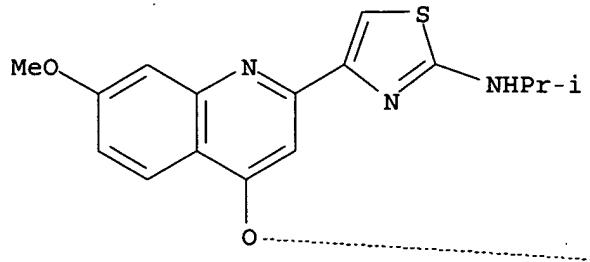
RN 300832-84-2 HCAPLUS

CN Cyclopropane[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic

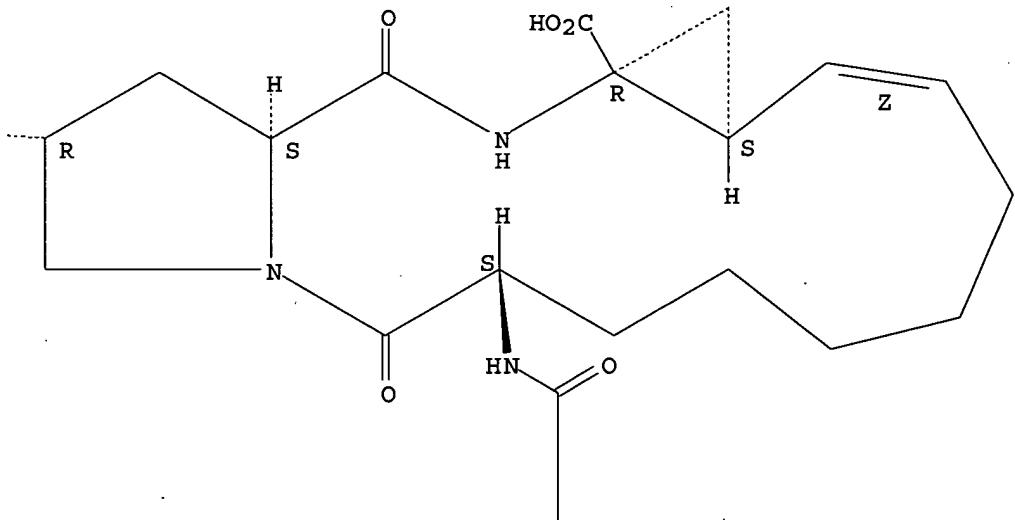
acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

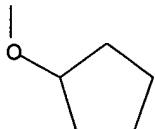
PAGE 1-A



PAGE 1-B



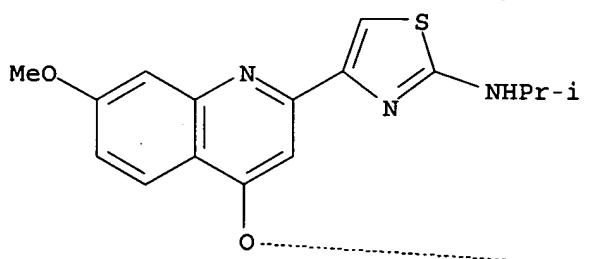
PAGE 2-B



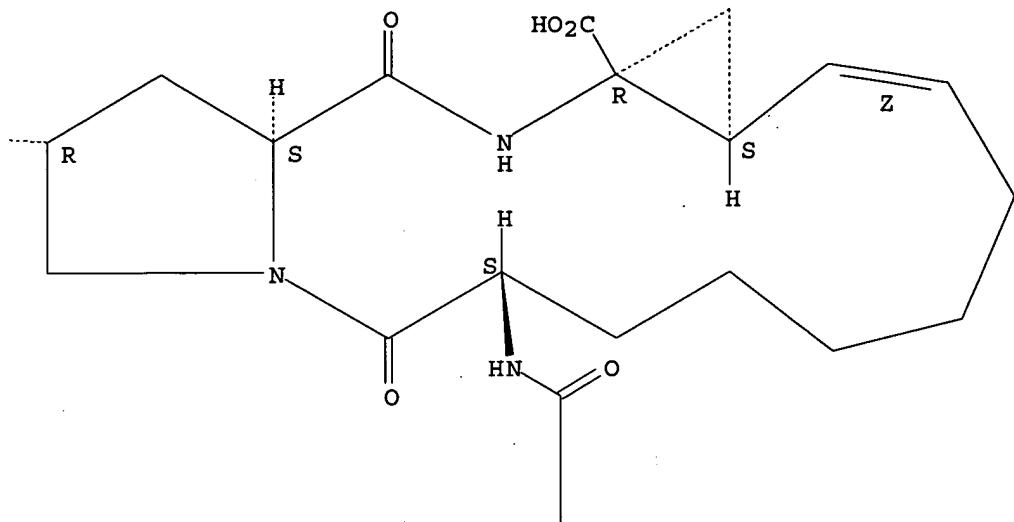
ACCESSION NUMBER: 2004:168624 HCAPLUS
 DOCUMENT NUMBER: 140:350045
 TITLE: Structure-activity study on a novel series of
 macrocyclic inhibitors of the hepatitis C virus NS3
 protease leading to the discovery of BILN 2061
 AUTHOR(S): Llinas-Brunet, Montse; Bailey, Murray D.; Bolger,
 Gordon; Brochu, Christian; Faucher, Anne-Marie;
 Ferland, Jean Marie; Garneau, Michel; Ghiro, Elise;
 Gorys, Vida; Grand-Maitre, Chantal; Halmos, Ted;
 Lapeyre-Paquette, Nicole; Liard, Francine; Poirier,
 Martin; Rheaume, Manon; Tsantrizos, Youla S.; Lamarre,
 Daniel
 CORPORATE SOURCE: Departments of Chemistry and Biological Sciences,
 Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S
 2G5, Can.
 SOURCE: Journal of Medicinal Chemistry (2004), 47(7),
 1605-1608
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB From the discovery of competitive hexapeptide inhibitors, potent and
 selective HCV NS3 protease macrocyclic inhibitors have been identified.
 Structure-activity relationship studies were performed focusing on
 optimizing the N-terminal carbamate and the aromatic substituent on the
 (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in
 the cell-based assay and with improved oral bioavailability in rats were
 identified. BILN 2061 was selected as the best compound, the first NS3
 protease inhibitor reported with antiviral activity in man.
 IT 300832-84-2P
 RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic
 preparation); BIOL (Biological study); PREP (Preparation)
 (BILN 2061; structure-activity study on a novel series of macrocyclic
 inhibitors of the hepatitis C virus NS3 protease leading to the
 discovery of BILN 2061)
 RN 300832-84-2 HCAPLUS
 CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic
 acid, 6-[[cyclopentyloxy]carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16
 ,16a-tetradecahydro-2-[[7-methoxy-2-[[1-methylethyl]amino]-4-thiazolyl]-
 4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA
 INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

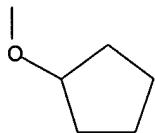
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:142968 HCAPLUS
 DOCUMENT NUMBER: 140:193056
 TITLE: Combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compositions, and use in the treatment of cytokine-mediated diseases
 INVENTOR(S): Simianer, Stefan; Bilbault, Pascal; Cappola, Michael L.; Way, Susan Lynn
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA; Boehringer Ingelheim France
 SOURCE: PCT Int. Appl., 168 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014387	A1	20040219	WO 2003-US25341	20030812
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
 TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004110755

A1

20040610

US 2003-638702

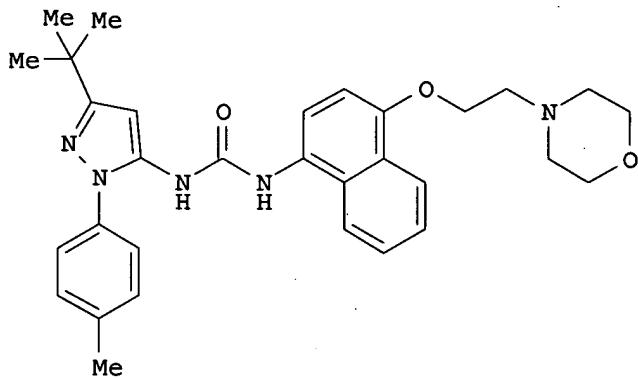
20030811

PRIORITY APPLN. INFO.:

US 2002-403115P

P 20020813

GI



AB The invention relates to pharmaceutical combination therapies based on p38 kinase inhibitors and another active ingredients, pharmaceutical compns. comprising such combinations, processes for preparing them, and their use in the treatment of cytokine-mediated diseases. Preparation of I (BIRB 796 BS) is described.

IT 300832-84-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

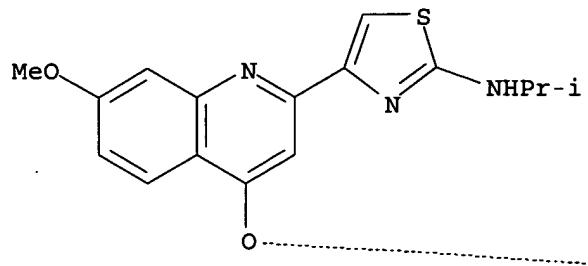
(combinations of active agents with p38 MAP kinase inhibitors, pharmaceutical compns., and use in treatment of cytokine-mediated diseases)

RN 300832-84-2 HCAPIPLUS

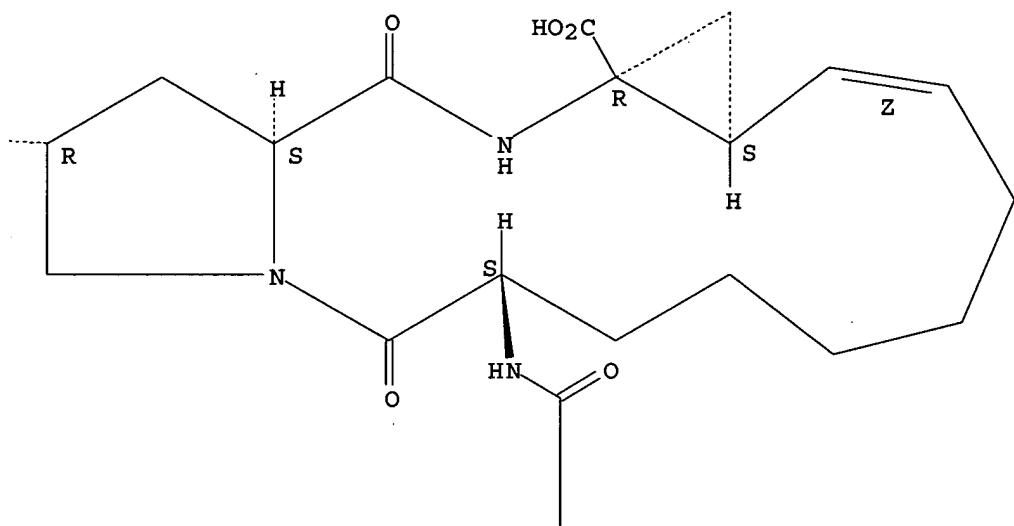
CN Cyclopropane[el]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

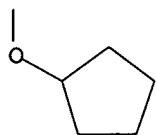
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:886572 HCAPLUS
 DOCUMENT NUMBER: 140:122161
 TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus
 Lamarre, Daniel; Anderson, Paul C.; Bailey, Murray;
 AUTHOR(S):

Beaulieu, Pierre; Bolger, Gordon; Bonneau, Pierre;
 Boes, Michael; Cameron, Dale R.; Cartier, Mireille;
 Cordingley, Michael G.; Faucher, Anne-Marie; Goudreau,
 Nathalie; Kawai, Stephen H.; Kukolj, George; Lagace,
 Lisette; LaPlante, Steven R.; Narjes, Hans; Poupart,
 Marc-Andre; Rancourt, Jean; Sentjens, Roel E.; St.
 George, Roger; Simoneau, Bruno; Steinmann, Gerhard;
 Thibeault, Diane; Tsantrizos, Youla S.; Weldon, Steven
 M.; Yong, Chan-Loi; Llinas-Brunet, Montse

CORPORATE SOURCE: Departments of Biological Sciences, Boehringer
 Ingelheim (Canada) Ltd, Laval, QC, H7S 2G5, Can.

SOURCE: Nature (London, United Kingdom) (2003), 426(6963),
 186-189

CODEN: NATUAS; ISSN: 0028-0836
 PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics. The HCV-encoded NS3 protease is essential for viral replication and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of BILN 2061, a small mol. inhibitor biol. available through oral ingestion and the first of its class in human trials. Administration of BILN 2061 to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

IT 300832-84-2, BILN 2061

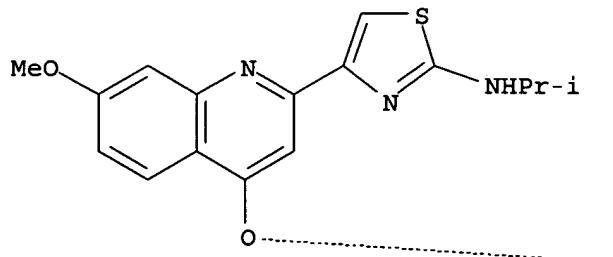
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus)

RN 300832-84-2 HCPLUS

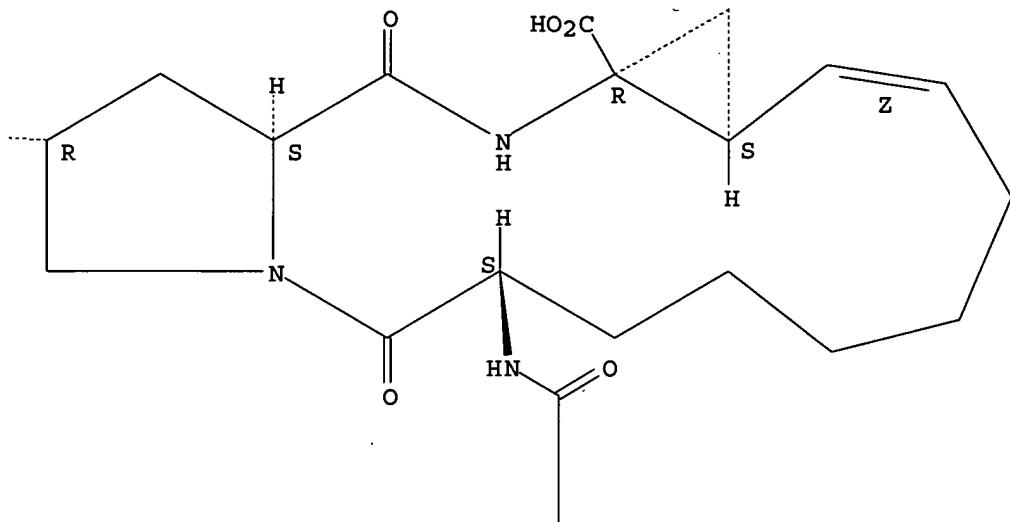
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyloxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

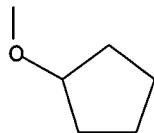
PAGE 1-A



PAGE 1-B



PAGE 2-B



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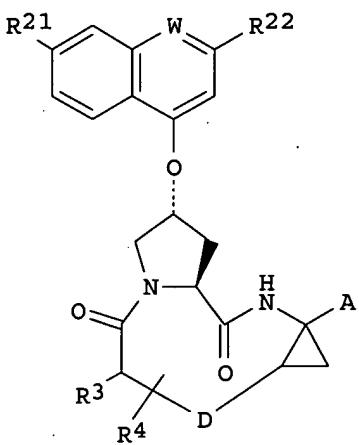
L8 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:648255 HCAPLUS
 DOCUMENT NUMBER: 139:197768
 TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
 INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-Marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-Brunet, Montse
 PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
 SOURCE: U.S., 90 pp., Cont.-in-part of U.S. Ser. No. 542,675, abandoned.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6608027	B1	20030819	US 2001-760946	20010116
EP 1437362	A1	20040714	EP 2004-9264	20000403

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, CY

US 2004002448 A1 20040101 US 2003-358726 20030205
PRIORITY APPLN. INFO.: US 1999-128011P P 19990406
US 2000-542675 B2 20000403
EP 2000-913999 A3 20000403
US 2001-760946 A1 20010116

OTHER SOURCE(S): MARPAT 139:197768
GI



AB Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroaryl amino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus. Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)- (Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μ M in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

IT 300832-84-2P 300832-97-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

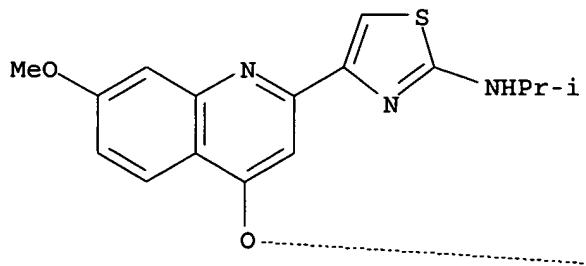
(preparation of macrocyclic peptides active against the hepatitis C virus)

RN 300832-84-2 HCPLUS

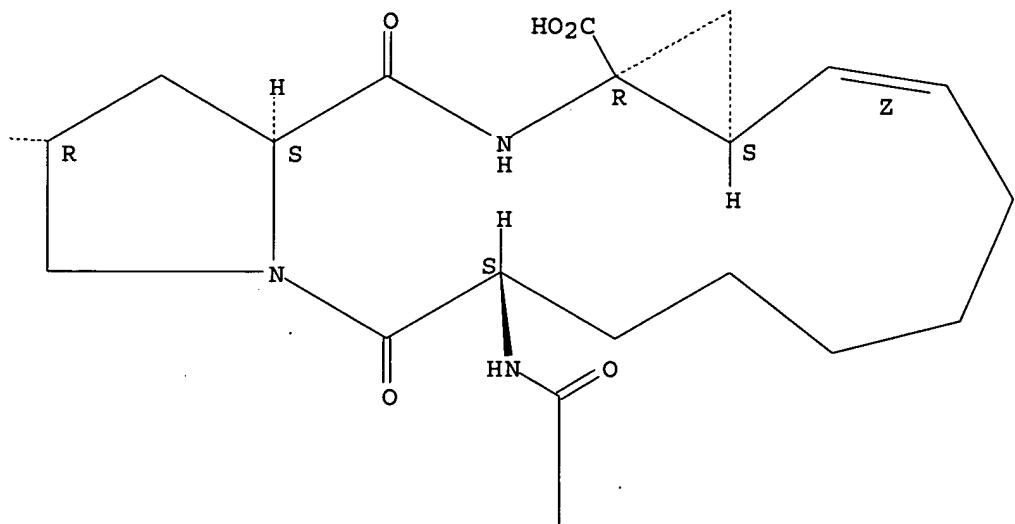
CN Cyclopropane[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-1,2,3,6,7,8,9,10,11,13*a*,14,15,16,16*a*-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2*R*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

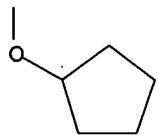
PAGE 1-A



PAGE 1-B



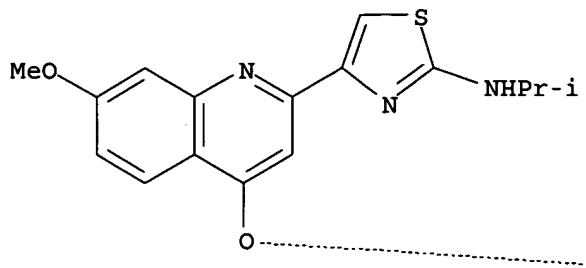
PAGE 2-B



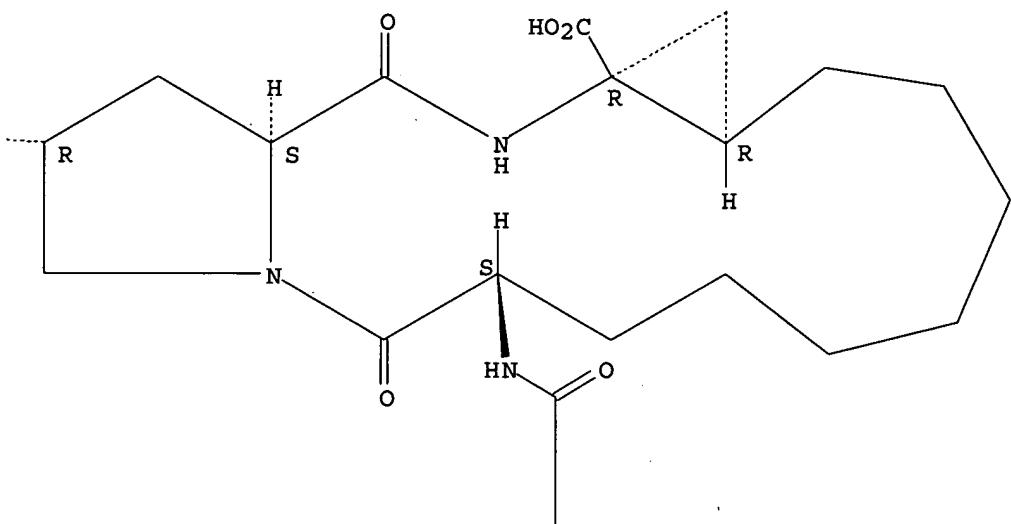
RN 300832-97-7 HCAPLUS
 CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[(cyclopentyloxy)carbonyl]amino]hexadecahydro-2-[[7-methoxy-2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,13aR,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

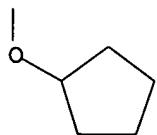
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:633516 HCAPLUS
 DOCUMENT NUMBER: 139:185670
 TITLE: Pharmaceutical compositions for hepatitis C viral protease inhibitors
 INVENTOR(S): Chen, Shirlynn; Mei, Xiaohui

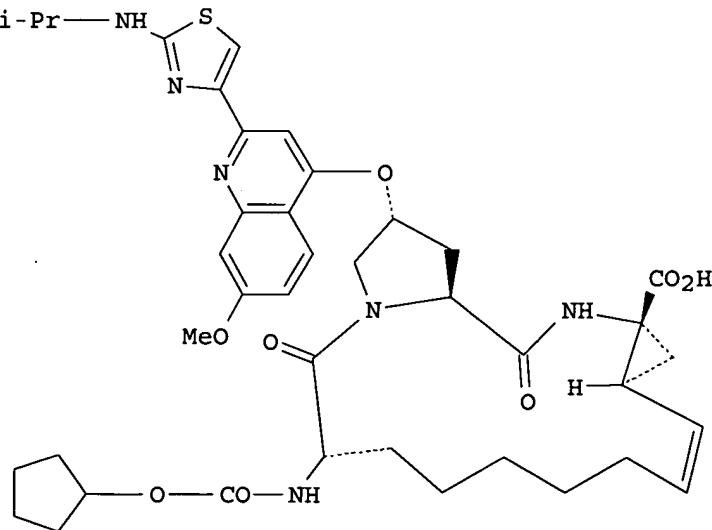
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066103	A1	20030814	WO 2003-US3380	20030205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003195228	A1	20031016	US 2003-357919	20030204
EP 1474172	A1	20041110	EP 2003-707713	20030205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
RIORITY APPLN. INFO.:			US 2002-355694P	P 20020207
			WO 2003-US3380	W 20030205

OTHER SOURCE(S) :

OTHER SOURCE(S): MARPAT 139:185670

GI



AB Disclosed are pharmaceutical compns. of hepatitis C viral protease inhibitors having improved bioavailability, and methods of using these compns. for inhibiting the replication of the hepatitis C virus (HCV) and for the treatment of an HCV infection. These compns. include co-solvent systems, lipid based systems, solid dispersions and granulations, and all comprise the hepatitis C viral protease inhibitor, at least one pharmaceutically acceptable amine and optionally one or more addnl.

ingredients. A composition contained I 4, tromethamine 3.2, water 44.8, ethanol 21.3, and propylene glycol 26.7 weight/weight%.

IT 300832-84-2

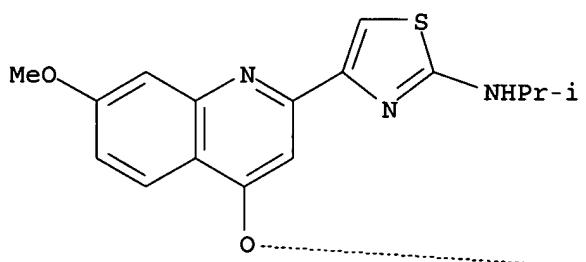
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for hepatitis C viral protease inhibitors)

RN 300832-84-2 HCAPLUS

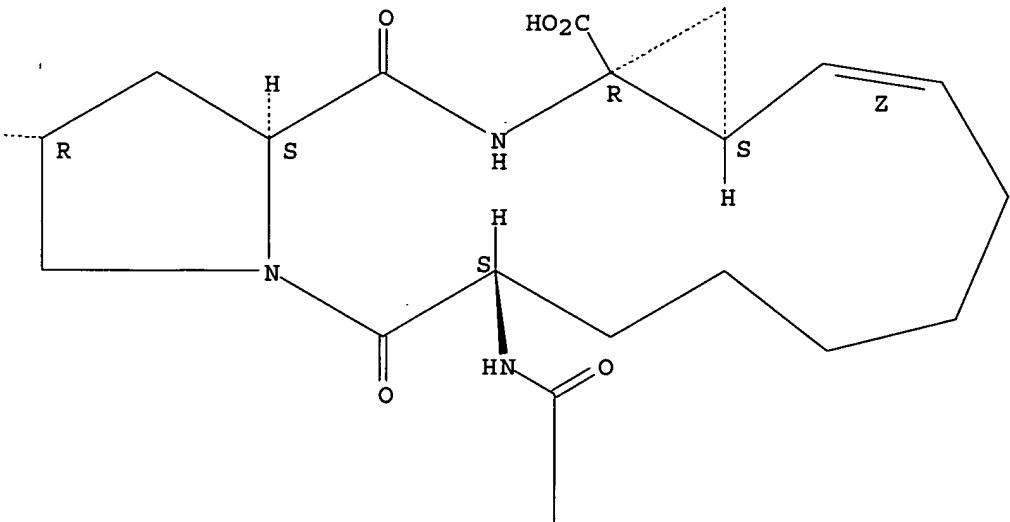
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[cyclopentyloxy carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

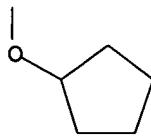
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:511084 HCAPLUS
 DOCUMENT NUMBER: 139:69527
 TITLE: Preparation of macrocyclic compounds as inhibitors of hepatitis C virus
 INVENTOR(S): Campbell, Jeffrey Allen; Good, Andrew Charles
 PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
 SOURCE: PCT Int. Appl., 225 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053349	A2	20030703	WO 2002-US39926	20021213
WO 2003053349	A3	20040115		
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PRIORITY APPLN. INFO.:			US 2001-344080P	P 20011220
			US 2002-382103P	P 20020520
			WO 2002-US39926	W 20021213

OTHER SOURCE(S): MARPAT 139:69527
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to macrocyclic compds. I [R1 = (cyclo)alkyl; R2 = H, halo, alkyl, alkoxy, cycloalkoxy, (un)substituted aryl or heterocyclyl; R3 = H, halo, CF₃, alkoxy, cycloalkoxy; R4 = NH₂ or NHR₆, where R₆ is alkanoyl, alkylaminocarbonyl, or carbalkoxy; Q is a 3-9 atom (un)saturated alkylene chain optionally containing 1-3 heteroatoms O, S, SO, or SO₂], including methods for their synthesis and use in pharmaceutical compns. for therapeutic or prophylactic prevention or treatment of hepatitis C

virus (HCV) infection. Thus, 3,13-diazatricyclo[11.3.0.04,6]hexadec-7-ene derivative II was prepared by a multistep procedure and assayed for inhibition of HCV NS3/4A protease ($IC_{50} < 5 \mu M$).

IT 300832-84-2P 552335-68-9P 552335-69-0P

552335-70-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

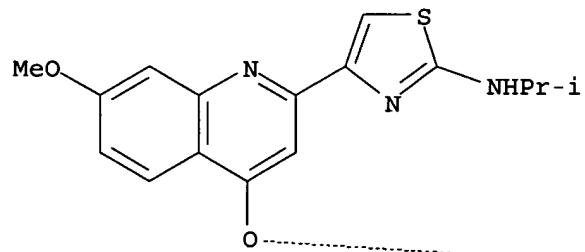
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RN 300832-84-2 HCPLUS

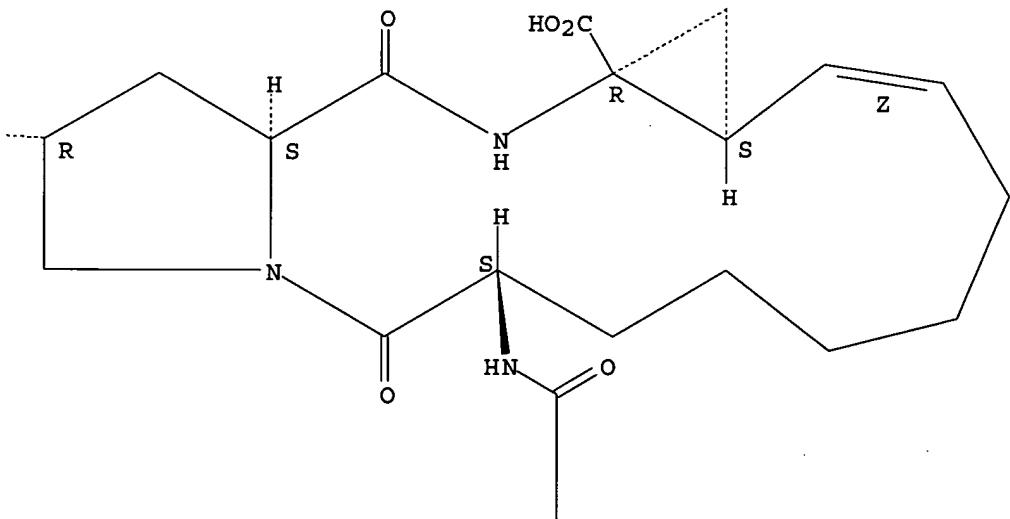
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Absolute stereochemistry.
Double bond geometry as shown.

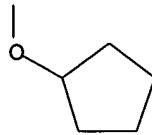
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PAGE 1-B



PAGE 2-B

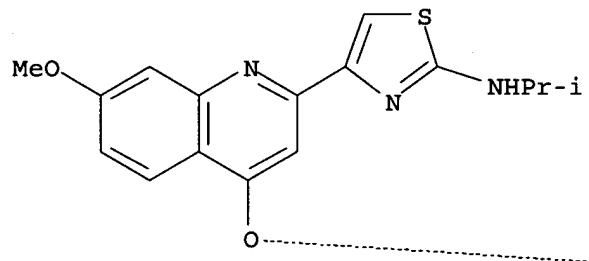


RN 552335-68-9 HCPLUS

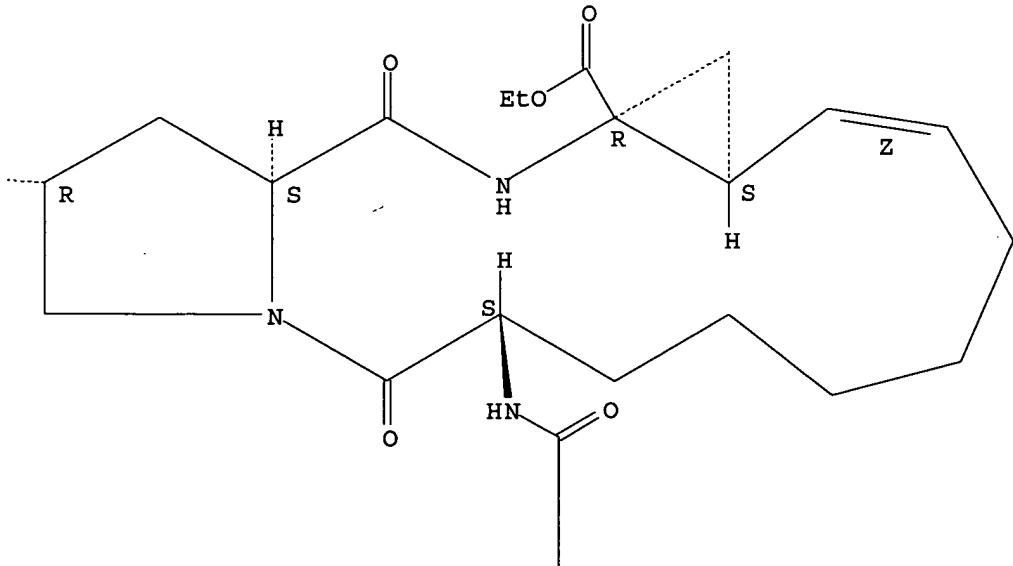
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Absolute stereochemistry.
Double bond geometry as shown.

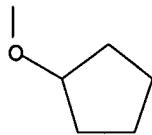
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PAGE 2-B

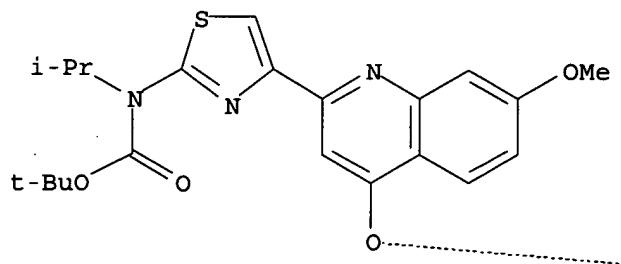


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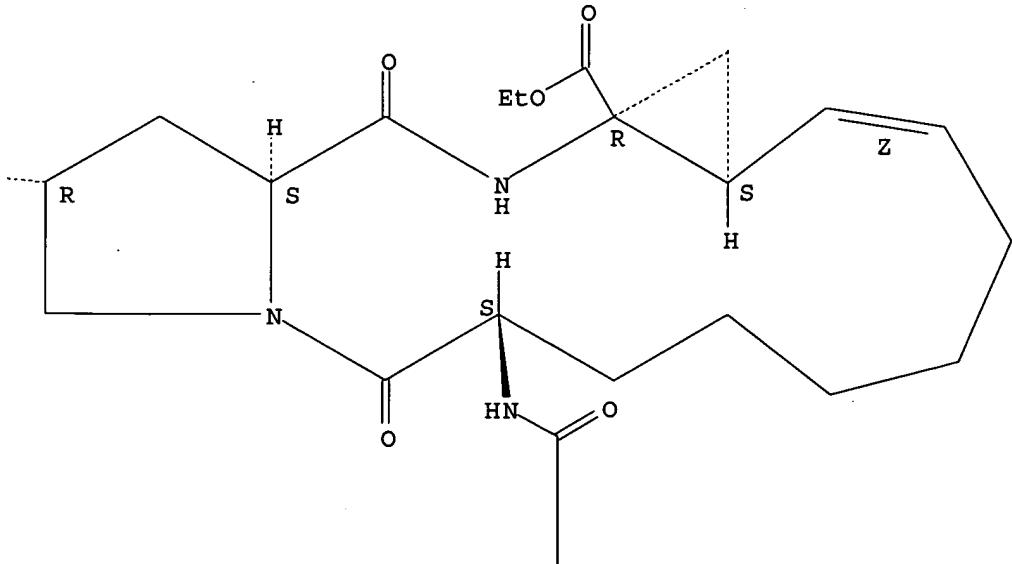
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-2-[[2-[[2-[[1,1-dimethylethoxy)carbonyl](1-methylethyl)amino]-4-thiazolyl]-7-methoxy-4-quinolinyl]oxy]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-5,16-dioxo-, ethyl ester, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

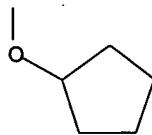
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PAGE 1-B



PAGE 2-B

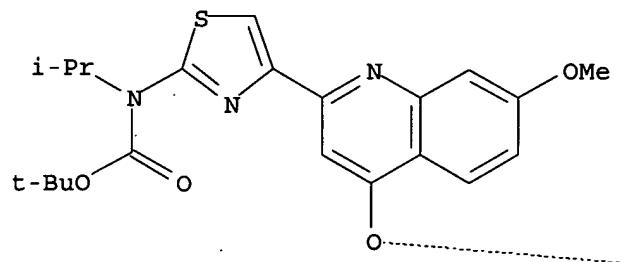


RN 552335-70-3 HCPLUS

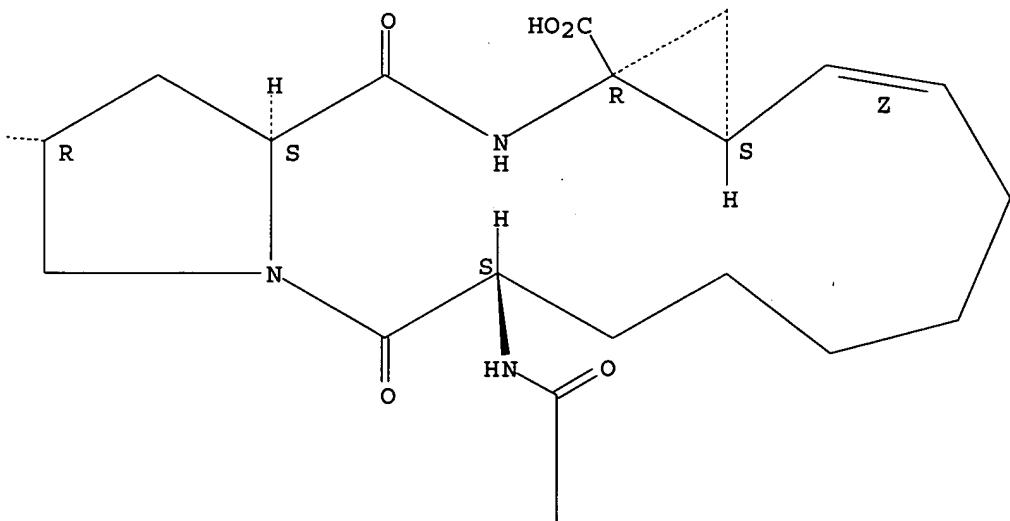
CN Cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylic acid, 6-[[[(cyclopentyloxy)carbonyl]amino]-2-[[2-[[2-[(1,1-dimethylethoxy)carbonyl](1-methylethyl)amino]-4-thiazolyl]-7-methoxy-4-quinolinyl]oxy]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-5,16-dioxo-, (2R,6S,12Z,13aS,14aR,16aS)- (9CI) (CA INDEX NAME)

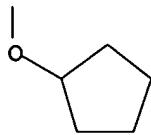
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

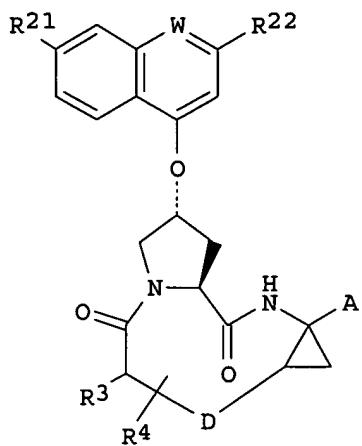




L8 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:725652 HCAPLUS
 DOCUMENT NUMBER: 133:296659
 TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
 INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-brunet, Montse
 PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
 SOURCE: PCT Int. Appl., 154 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059929	A1	20001012	WO 2000-CA353	20000403
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TR 200102878	T2	20020121	TR 2001-200102878	20000403
EE 200100516	A	20021216	EE 2001-516	20000403
NZ 515286	A	20040227	NZ 2000-515286	20000403
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NO 2001004857	A	20011031	NO 2001-4857	20011005
PRIORITY APPLN. INFO.:			US 1999-128011P	P 19990406
			EP 2000-913999	A3 20000403
			WO 2000-CA353	W 20000403

OTHER SOURCE(S): MARPAT 133:296659
 GI



I

AB Macrocyclic peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH₂, aryl- or heteroaryl amino, NHCOR₃₂, CONHR₃₂, CO₂R₃₂, where R₃₂ is alkyl or cycloalkyl; D is a 5 to 10-atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the hepatitis C virus. Thus, macrocyclic peptide I [W = N; R21, R22, R4 = H; A = CO₂H; R3CH-D = (S)-(Me₃CO₂CNH)CH(CH₂)₃CH:CH(CH₂)₂-E (syn to acid)] was prepared and showed IC₅₀ > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

IT 300832-84-2P 300832-97-7P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

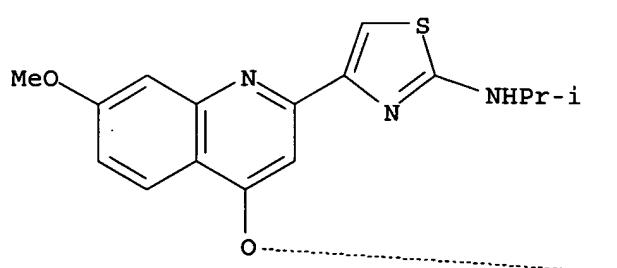
(preparation of macrocyclic peptides active against the hepatitis C virus)

RN 300832-84-2 HCPLUS

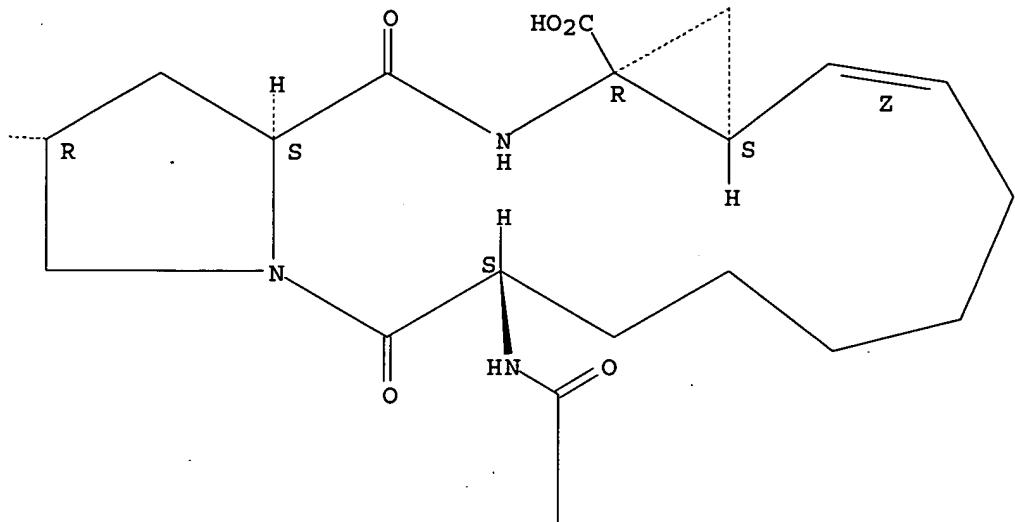
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Absolute stereochemistry.
Double bond geometry as shown.

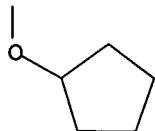
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PAGE 1-B



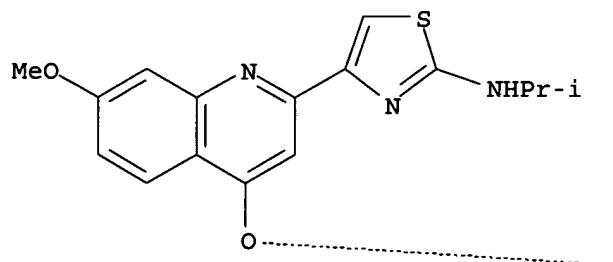
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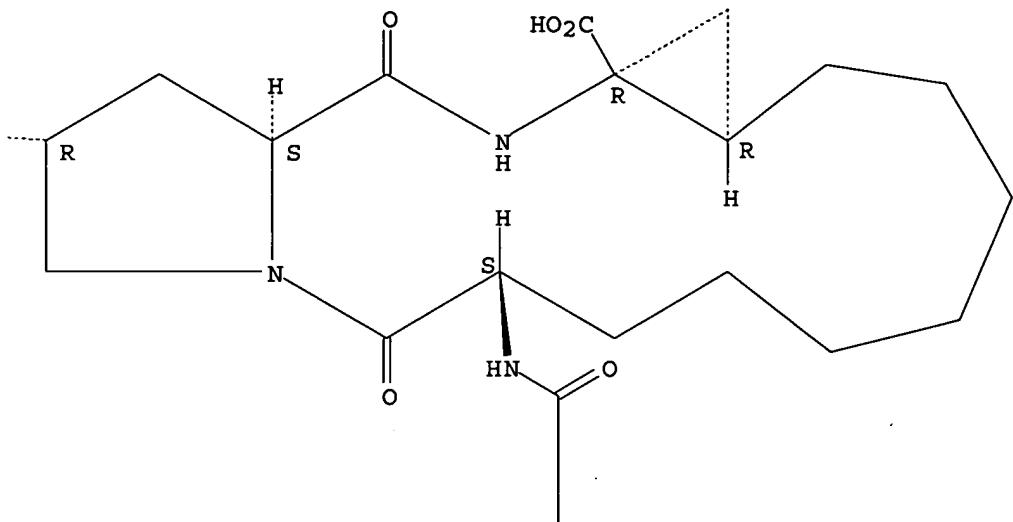
RN 300832-97-7 HCAPLUS
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Absolute stereochemistry.

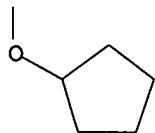
PAGE 1-A



PAGE 1-B



PAGE 2-B



REFERENCE COUNT:

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